

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re patent application of

J. Peart et al.

Serial No. 10/759,280

Filed: January 20, 2004

Confirmation No.: 6861

Group Art Unit 1616

Examiner: Alstrum Acevedo, James Henry

For: ***Δ⁹ TETRAHYDROCANNABINOL (Δ⁹ THC) SOLUTION METERED DOSE
INHALERS AND METHODS OF USE***

MAIL STOP APPEAL BRIEF

Commissioner for Patents

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APPELLANTS' REPLY BRIEF

As suggested in the Appeal Brief (p. 13), Claim 61 is a good starting point, because there has been a blatantly incorrect obviousness rejection of the claimed inventive method of aerosolizing a tetrahydrocannabinol ("THC"), comprising dissolving a THC in a hydrofluoroalkane (HFA) and forming a stable pharmaceutical composition; and aerosolizing the stable pharmaceutical composition into respirable droplets comprising the THC. The references relied upon by the Examiner are very removed from such an inventive method. The Examiner's Answer admits¹ some deficiencies in the prior art, but persists in arguing (p. 12) that "both Mechoulam and Volicer suggest inhalation formulations of THC", relying on cols. 4 and 5 of Volicer. However, neither

¹The Examiner's Answer (pp. 7, 10) admits that "Mechoulam and Volicer lack an explicit teaching of aerosol formulations comprising hydrofluoroalkanes [HFAs]" and that "Pars et al. lack a teaching of aerosol formulations comprising a hydrofluoroalkane [HFA]." The Examiner's Answer (p. 8) admits that "Mechoulam or Volicer and McNally lack the teaching of compositions comprising pharmaceutically acceptable salts of tetrahydrocannabinol [THC]."

Mechoulam nor Volicer is the requisite enabling disclosure² of an inhalation formulation of THC. No reference teaches to dissolve THC in an HFA, nor to form a stable pharmaceutical composition from THC dissolved in HFA, nor to aerosolize a stable pharmaceutical composition into respirable droplets comprising THC. But undeterred, the Examiner's Answer (p. 20) makes the conclusory and incorrect allegation that "it has properly been demonstrated that the combined prior art necessarily suggests the preparation of solution aerosol formulations comprising THC, HFA, and ethanol with a reasonable expectation of success." That is simply not so.

The rejection has not fairly and objectively brought to life the thinking of a person of ordinary skill in the art at the time of Applicants' invention, and that is largely because the rejection has refused to take into account many facts which would have been in the head of such a person, and which the Appeal Brief sets forth as being **factual findings** that should be admitted by the Examiner, and recognized as contributing to the knowledge, experience and mode of thinking of a person of ordinary skill in the art. The Examiner's Answer is based on treating the hypothetical person of ordinary skill in the art as someone with highly simplistic thinking, that peculiarly would seize on one or two arbitrary facts, while for some reason wearing blinders to all the pertinent literature. This is just not a fair approach to the person of ordinary skill in the art, who takes in more nuances and facts than the Examiner's Answer gives him or her credit for, and is aware of, not blind to, the literature in the art. That is a fundamental overall problem with the obviousness rejections, which can be seen time and again by looking at, for example, the following aspects addressed in the Appeal Brief:

1) As of the filing of the application, there was no pharmaceutically acceptable aerosol form of Δ^9 THC (Spec. 9:4); 2) In Mechoulam, Volicer, Pars and McNally, there is not one actual example of a THC aerosol. These facts are not rebutted in the Examiner's Answer (p. 13). Each such fact should be admitted, and then given proper weight.

3) In the four references, the only actual example of an aerosol is the Butixocort

²See, e.g., *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 297 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986).

Propionate aerosol in McNally; 4) The structures of THC and Butixocort Propionate substantially differ. (App. 6-7, para. 19.) Again, these facts are not rebutted in the Examiner's Answer (p. 14). The Examiner seems to get hung up with narrowing his focus to **one** aspect for which he sees commonality between THC and butixocort while artificially wearing blinders to **all** the aspects such as structure. The Examiner's Answer (p. 14) does not deny the substantial structural difference between THC and Butixocort Propionate. The Examiner's Answer neglects to recognize the structural differences, and neglects to accord proper weight and reasonable analysis to the structural differences. 5) *The solubility of THC cannot be inferred from the solubility of Butixocort Propionate.* Again, the Examiner's Answer does not rebut this fact, but rather, simply omits to properly account for this fact.

6) *THC and Butixocort Propionate cannot be considered interchangeable by a person of ordinary skill in the art for purposes of aerosol formulation.* (App. 5-6, para. 14, 18.) The Examiner's Answer (p. 14) essentially disputes this fact, but based only on the Examiner's own say-so and not on any evidence. The Declaration evidence of record in support of this requested factual finding is entitled to more weight than the Examiner's own unsupported theory. The Examiner's theory only establishes *prima facie* obviousness, and the Examiner cannot simply revert to his own theory in the presence of Declaration evidence of record contradicting his theory.

7) *The properties of THC are unlike the properties of drugs that generally have been formulated into aerosols.* (App. 5-6, para. 14.) The Examiner's Answer (pp. 14-15) does not rebut this fact. Clearly this fact has been given insufficient weight. From this fact, that the properties of THC are unlike the properties of drugs that generally have been formulated into aerosols, the proper and reasonable inference is that a person of ordinary skill in the art at the time of the claimed invention did not expect to be able to formulate THC into an aerosol. How could a person of "ordinary" skill in the art possibly think that he could formulate THC into an aerosol when nobody else, including those of greater skill, was having any success doing so?

8) *The difficulty of working with THC was well documented in the literature* (App. 5-6, para. 14); 9) *The large dosage amounts of THC required for systemic administration of*

THC were well documented in the literature (id.); 10) The properties of THC that make it unlike, and not interchangeable with, other drugs were well documented in the literature (id.). The Examiner's Answer (p. 15) does not rebut these facts. These facts have been given insufficient weight as the Examiner's Answer persists in trying to prop-up the artificial hindsight reconstruction of the claimed invention. From these facts about what was well documented in the literature, which is imputed to the hypothetical person of ordinary skill in the art, the proper and reasonable inference is that a person of ordinary skill in the art thought that THC was difficult to work with, and thought THC not interchangeable with other drugs.

11) THC was known to resemble rubber-cement rather than a powder (App. 5-6, para. 14.); 12) Most drugs resemble a powder, not rubber-cement (id.); 13) A further known difficulty in working with THC was the inability to grind THC (a resinous material) into a microfine powder (id.); 14) In formulations that contain drug substance suspended in propellant usually the drug is ground to a microfine powder before incorporation into the propellant mixture, but THC as a resinous material cannot be ground into a microfine powder (App. 6, para. 15-16). The Examiner's Answer (pp. 15-16) does not rebut these facts. Rather, the Examiner's Answer fails to appreciate the significance of each fact, such as the insurmountable technical problem of the non-aerosolizability of something that resembles rubber-cement. The Examiner's Answer fails to process each of these facts in the way that a person of ordinary skill in the art would have thought.

15) A person of ordinary skill in the art would not view THC as sufficiently soluble or stable to be used in a formulation to achieve necessary metered and respirable doses. (App. 6, para. 17; see also Spec. 9:11, that THC is known to deteriorate during storage; id., para. bridging pp. 10-11.) The Examiner's Answer (p. 16) opposes this requested factual finding. Prof. Peart's analysis of the solubility and stability problems of THC is more detailed and analytical and is scientifically reasonable, which cannot be said about the simplistic (and now-rebutted) conclusory theory of the Examiner's.

16) There is no prior art in which THC was formulated with HFA; 17) There is no prior art in which THC was dissolved in HFA; 18) There is no prior art in which a THC aerosol was formulated without CFC; 19) There is no prior art in which respirable

droplets of THC were formulated without CFC. The Examiner's Answer (p. 16) does not rebut these requested factual findings. Rather, once again, the issue is that the rejection does not properly account for how these facts would have affected the thinking of a person of ordinary skill in the art.

20) *A THC-CFC-ethanol formulation having 23% ethanol would fail to produce respirable particles* (Spec. 9:12-13). The Examiner's Answer (pp. 16-17) does not rebut this fact.

21) *Before Applicants' invention, a person of ordinary skill in the art lacked knowledge of how to aerosolize THC without CFC.* The Examiner's Answer (p. 17) opposes this requested factual finding. We submit that the Examiner's Answer (p. 17) has reached incorrect conclusions about the knowledge of a person of ordinary skill in the art.

22) *Interest in pharmaceutical THC dates back ~ 30 years* (App. 40-41, para. 9);
23) *Applicants were the first to formulate a non-CFC THC aerosol.* The Examiner's Answer (p. 17) does not rebut these facts. Too little weight has been given to the fact that no one before Applicants formulated a non-CFC THC aerosol. The Examiner's theory seems, strangely, to be that it was obvious to a person of ordinary skill in the art how to formulate a non-CFC THC aerosol and they all just did not bother to actually do so. That is completely peculiar thinking to propose for a person of ordinary skill in the art, because a non-CFC THC aerosol would be a highly commercial technology, and if a person of "ordinary" skill in the art could have simply whipped up such an aerosol, they would have done so at the beginning of the 30 years mentioned, and not have needed to wait for Applicants to invent the presently claimed invention.

24) *The Mechoulam actual example is not an aerosol.* The Examiner's Answer (p.18) does not dispute this. The Examiner's Answer takes insufficient account of the fact that a person of ordinary skill in the art when reading a patent thinks differently about actual formulation examples than about other parts of the specification.

25) *The Mechoulam actual example is not aerosolizable;* 26) *The Olsen reference confirmed the difficulties of formulating THC known by one of ordinary skill in the art.* (App. 5, para. 13.) The Examiner's Answer omits to discuss these facts.

27) *The Olsen reference teaches an inhalation aerosol of THC in 3 ml alcohol,*

0.068 g Arlacel surfactant and 7.5 g CFC propellant (App. 5, para. 13); 28) The Olsen reference states "Formulations of THC are difficult to prepare because of water insolubility and also because of the tacky nature of the pure material at room temperature. Early experiments demonstrated excellent solubility of THC in conventional ethanol-difluorodichloromethane [propellant 12] - tetrafluorodichloro-ethane [propellant 114] solvent systems. Attempts at evaluation of these dosage forms in animals, however, indicated excessive tack of the spray and hence poor transport to the lungs." The Examiner's Answer (p. 18) does not rebut these facts, but rather, wants to ignore them. It would be error to ignore Olsen, because Olsen affected the thinking of a person of ordinary skill in the art. The Examiner's Answer (p. 18) does not dispute that Olsen says what we mentioned. Rather, the Examiner's Answer proposes to ignore Olsen because of the Examiner's own unsubstantiated theory that "the water solubility of THC is not an important consideration in the formulation of non-aqueous aerosol compositions". Olsen is part of the pertinent literature that is imputed to the person of ordinary skill in the art and cannot be disregarded simply because it calls into further question the Examiner's theory.

29) The initial promise of a THC aerosol according to Olsen et al. (1975) never materialized, and in the past few decades, before Applicants' invention, it was conventionally thought that THC was not suited for aerosol-dispensing (Spec., sent. bridging pp.10-11); 30) One of ordinary skill in formulating THC would be aware of the long-standing lack of success in developing a THC aerosol. (App. 5, para. 13.) The Examiner's Answer (pp.18-20) does not offer any evidence to the contrary.

31) The actual experimentation of which a person of ordinary skill in the art at the time of Applicants' invention would have been given much greater weight than, and would have over-ridden, the generalized casual sentences in Mechoulam and Volicer which were unattached to any actual aerosol experimentation. (App. 5, para. 13.) The Examiner's Answer (p.20) disagrees with Dr. Peart's Declaration. However, Dr. Peart's evidence is in accord with the normal and usual thinking of scientists reading patents, and this point of disagreement cannot be resolved in the Examiner's favor.

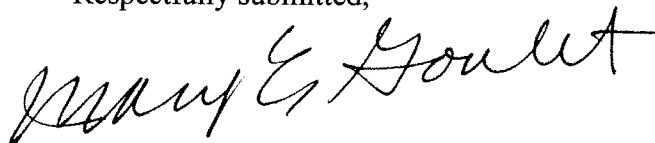
32) Disadvantages of the oral form of THC (MARINOL) were known. (Spec., para. bridging pp. 6-7.) The Examiner's Answer (p. 20) does not dispute this fact.

It is error for the Examiner to have avoided making each of these factual findings, and error for the Examiner to rely on an alleged idiosyncratic thought process that is out-of-line with how a person of ordinary skill in the art thought.

Moreover, the Examiner's Answer (p. 21) refuses to recognize that (regarding the composition claims) indeed it is proper for Applicants to compare their claimed inventive composition to the actual example in the primary reference. The Examiner's Answer (p.21) states that "Appellants seem to regard Volicer's explicit suggestion of THC-dichlorofluoromethane aerosol formulations as not an example". THC-dichlorofluoromethane aerosol formulation exists only in the Examiner's mind, not as an example in Volicer. The example in Volicer is Dronabinol (which is not an aerosol).

With regard to each of the claims on appeal, the *prima facie* case of obviousness has been rebutted by Applicants. It is respectfully submitted that the obviousness rejections cannot be maintained.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Mary E. Goulet", written in a cursive style.

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